Cardio-respiratory variability of healthy young subjects

Cite as: AIP Conference Proceedings **2348**, 030003 (2021); https://doi.org/10.1063/5.0051115
Published Online: 30 April 2021

Antonio Barajas-Martínez, Geraldine Tello-Santoyo, Pablo Berumen-Cano, Adriana Robles-Cabrera, Juan Antonio López-Rivera, Ruben Fossion, Juan Claudio Toledo-Roy, Alejandro Frank, Bruno Estañol, and Ana Leonor Rivera

Cardio-respiratory Variability of Healthy Young Subjects

Antonio Barajas-Martínez[1,2,3], Geraldine Tello-Santoyo[1,2], Pablo Berumen-Cano[1,2], Adriana Robles-Cabrera[1,2,3], Juan Antonio López-Rivera[1,4], Ruben Fossion[1,5], Juan Claudio Toledo-Roy[1,5], Alejandro Frank[1,5,6], Bruno Estañol[1,7], and Ana Leonor Rivera[1,5,a]

[1]*Centro de Ciencias de la Complejidad, UNAM, Mexico City, Mexico.*

[2] *Facultad de Medicina, UNAM, Mexico City, Mexico.*

[3]*Programa de Doctorado en Ciencias Biomédicas, UNAM, Mexico City, Mexico.*
[4]*Facultad de Ciencias,UNAM, Mexico City, Mexico.*

[5]*Instituto de Ciencias Nucleares, UNAM, Mexico City, Mexico.*
[6]*El Colegio Nacional, México, Mexico City, Mexico.*

[7]*Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico.*

[a] *corresponding author*: ana.rivera@nucleares.unam.mx.

Abstract. Young men have high cardio-respiratory variability reflecting the balance between robustness and adaptability to environmental and internal changes that characterize health. However, there are few biomarkers of this variability, thus it is important to determine the ranges for healthy men. Moreover, the health condition of women has considerable correlations with their menstrual cycle. Nevertheless, there is no complete characterization of how this cycle affects the overall physiological state, in particular the cardio-vascular and respiratory variability. To quantify these changes, cardio-respiratory time-series of young subjects are recorded daily during one month to determine the respiratory and heart-rate variability. As an initial proof of concept, four males (control group) and four females performed three maneuvers (clinostatism, rhythmic breathing at 0.1 Hz, and orthostatism) on a 5-minute interval. We also collected data on the circadian rhythm through physical activity and skin temperature. Females' menstrual cycle phase is determined from a clinical interrogation, physiological indicators of the cycle (cervical mucus fluidity and temperature elevation) and hormone determination by blood and urinary samples. Physiological time series of heart rate and breathing dynamics are less variable in women than in men, maybe due to the protective function of hormones, but to have conclusive remarks requires a study on a larger population.

Keywords: Network physiology, menstrual cycle, homeostasis, cardiorespiratory coupling, controlled rhythmical breathing

INTRODUCTION

Human health is characterized by robustness, supported by systems that allow it to maintain homeostasis and survive in a wide range of conditions, but also by its ability to rapidly and effectively adapt to a changing external environment [1,2]. This balance between robustness and adaptability can be measured by biomarkers in the time [3] and frequency domains [4] reflecting distinctive physiological responses [5,6]. Alterations in these biomarkers may appear before symptoms arise and opens up promising possibilities for applications in preventive medicine [7].

One of the unsolved paradoxes in medicine is that women have a longer life expectancy than men but they have a more fragile health. Unfortunately, the effect of the menstrual cycle in women in physiology has been largely neglected in research, even when it is known that the menstrual cycle is a vital sing for assessing the overall health status of a patient [8]. However, menstrual cycle by itself has an extensive impact on the physiology, from widespread effects regarding immune system signaling (IL-6, cortisol, CRP) [9,10], to hemostatic variables (VWF and FVIII) [11] and insulin resistance [12]. These effects, some of which may still be unknown, change whole body physiological

Proceedings of the XVI Mexican Symposium on Medical Physics
AIP Conf. Proc. 2348, 030003-1–030003-6; https://doi.org/10.1063/5.0051115
Published by AIP Publishing. 978-0-7354-4094-4/$30.00

adaptation to the environment like exercise recovery [13] and stress responses [14]. These changes also result in improvement or aggravation of several chronic diseases, like inflammatory bowel disease and asthma, that are labile to hormonal phases of the menstrual cycle [10]. Not only disease manifestations are affected by the menstrual cycle, but medical treatment may also be facilitated or impaired due to changes in the pharmacokinetics and pharmacodynamics [15]. Besides humans, very few species have menstrual cycles characterized by the cyclical shedding of the inner lining of the uterus, and in consequence animal models may not be suitable for its research [10]. On the other hand, there are contradictions in the literature about the effect of the menstrual cycle in the cardiovascular response [16,17]. Meanwhile, its effect on the respiratory response has not been studied at all. For this reason, it is pertinent to carry out a study that evaluates both parameters deeply and jointly. Our goal is to study the effect of female hormones on physiological time series and their relation to health. As a preliminary work, here we present the initial results of the protocol to understand heart rate variability, cardio-respiratory and cardio-vascular changes during the menstrual cycle on healthy women.

METHODOLOGY

Over the course of one month (from Monday to Friday at 7:00 a.m.) we performed non-invasive physiological tests in two groups: one formed by 4 women (18.6 ± 0.8 years old, with BMI 21 ± 3); and the other consisting of 4 men (20 ± 1 years old, with BMI 25 ± 5). All of them undergraduate university students of the UNAM, that did not smoke, had no cardiac diseases, and did not take medication. They were not hypertensive and had blood pressure levels of 120/80 mmHg or less. All subjects provided written informed consent, underwent a clinical history and physical examination. The Ethics' Committee of Facultad de Medicina, UNAM approved the protocol for data recording with the register FM/DI/023/2014. Subjects abstained from caffeine, beta-blockers, anticholinergics, antihistamines, opioids and adrenergic medication for the 24 hours and have a fast of at least 8 hours before the test.

The test consisted of: an initial 5-minute adequation on supine position, and a continuous recording of 5 minute evaluating three maneuvers: clinostatism, rhythmic controlled breathing at 0.1 Hz, and orthostatism. The instruments used to collect the data were: a Masimo MightySat™ fingertip pulse oximeter which recorded oxygen saturation (SpO_2), HR, RR pulse, and perfusion index; and a Bioharness®, that allows to record simultaneously heart rate (HR), breathing rate (BR), skin temperature, posture, and activity. The continuous heart rate monitoring system known as Bioharness, has in-band recording electrodes, whose correspondence is between the V3 and V4 leads of the conventional electrocardiogram, its use has been validated for monitoring heart rate, respiratory rate and accelerometry, among other variables [18]. Additionally, for all the subjects we have one record during the test taken with a Portapres device®, that register simultaneously the blood pressure and the heart rate [19]. Moreover, a Kronowise® was also used on the wrist for 24 hours during the month of the study, to monitor the circadian rhythm of physical activity and the skin temperature.

In order to determine the menstrual cycle phase of the female participants, we employed three complementary approaches, clinical interrogation, physiological indicators of the cycle and hormone determinations. As part of the clinical interrogation the date of last menstruation was logged, along with regularity of the previous cycles and menses duration, use of contraceptives, other medications or menstrual abnormalities, also other important conditions that can affect these cycles (polycystic ovary syndrome, for example). Two physiological indicators of the cycle were intensively monitored, cervical mucus fluidity and temperature elevation. After a training session, each participant self-reported their cervical mucus characteristics according to the Billings Method for assessment of the ovulation day [20,21]. Body temperature was continuously monitored the full duration of the experiment, one month in total [22]. Additionally, blood samples were drawn at three different points of the cycle, early follicular phase, preovulatory phase and mid-luteal phase for quantification of three characteristic hormone levels, testosterone, estradiol and progesterone [23]. In order to identify the ovulation day, daily urine samples were taken during the midcycle days to detect the LH surge [24]. The database with the records of the participants is available on the website of C3, UNAM.

RESULTS AND DISCUSSION

A typical physiological time series recorded with the Bioharness and the oximeter during the maneuvers is shown in Fig. 1. Data corresponds to a healthy 19 years old woman. There are noticeable changes on heart and respiratory rates, oxygenation and perfusion index. The change of position from supine to standing upright is seen as a vertical line on the position panel of Fig. 1, and rhythmic breathing produce sinusoidal changes on the breast position. Position variable allows us to clearly stablish the moments of each maneuver. On clinostatism, perfusion index, heart and

breath rates have variability, while SpO_2 is almost constant. Breathing rhythmically at 0.1 Hz is verified by a constant breathing rate of 6 bpm, and a resonance periodic rhythm on the heart rate and perfusion index, maintaining the oxygen saturation constant. During orthostatism, breath and heart rate have higher variability, heart rate almost doubles its average value and the perfusion index drops drastically. An overall similar heart rate and breathing dynamic is also observable in males Fig. 2. The variability changes can be studied not only on the time domain (with statistics and histograms), but also in frequency through the slope of the Power Spectral Density (PSD) on log-log, the areas under the Fourier transform on the low-frequency (LF) and high-frequency (HF) regions and the Poincaré plots (Fig. 2). Variability changes along these maneuvers show cardiorespiratory adaptability to changing physiological circumstances. Time-series with less variability suggest a system with increased robustness. At this early stage of our study we observe a tendency to greater cardio-respiratory variability in males, however our sample remains small for a more definite conclusion.

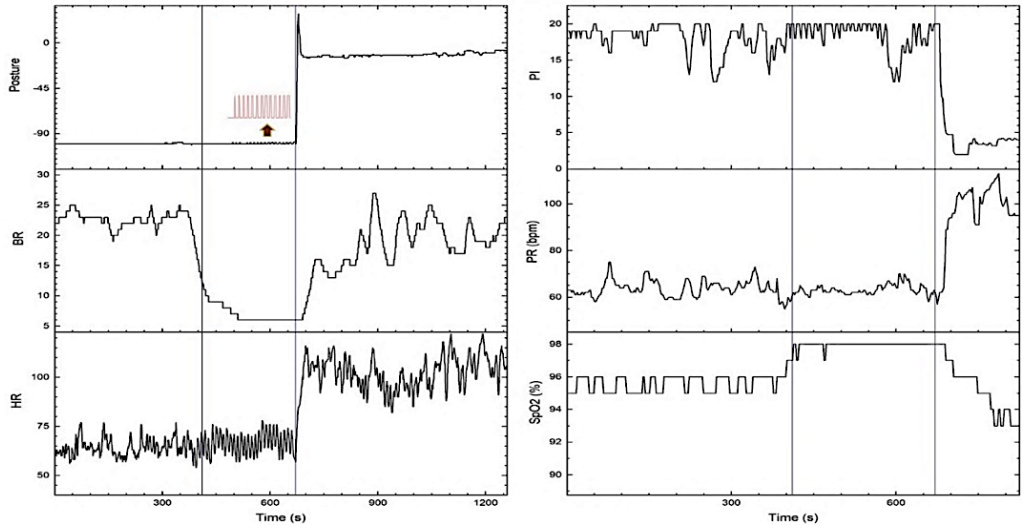

FIGURE 1. Typical physiological time-series records. Left correspond (from top to bottom) to posture, breathing and heart rate; while right show perfusion index, perfusion rate and oxygen saturation. Initially the subject is on clinostatism, then on supine position breathing rhythmically at 0.1 H (interval between vertical lines), and finally stands upright.

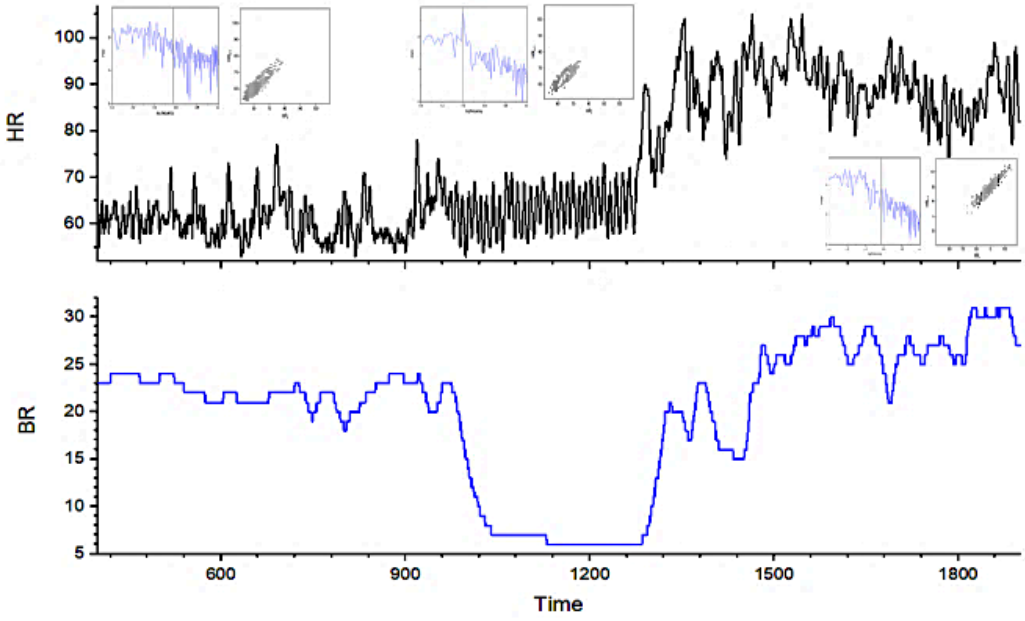

FIGURE 2. Respiratory and heart rate of a 19-year old, male control subject. Insets are the PSD and Poincaré plots of the 3 maneuvers: supine resting, breathing rhythmically at 0.1 Hz, and standing up.

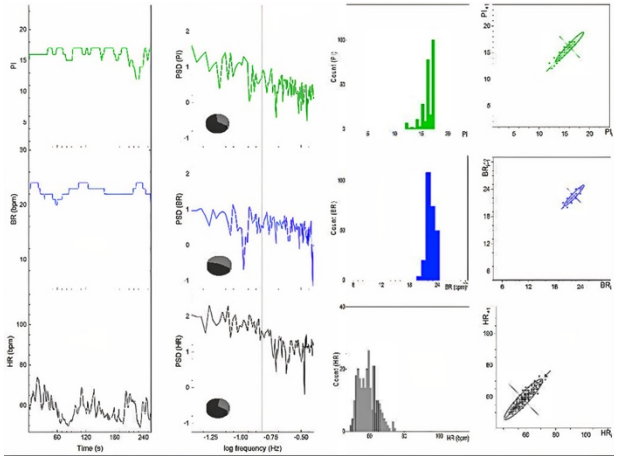

FIGURE 3. Typical physiological time-series records on clinostatism. From top to bottom appears perfusion index (PI), breathing rate (BR) and heart rate (HR). From left to right are the time series, its PSD with a vertical line at 0.15 Hz, and an inlet circle that corresponds to the proportion of LF (black) and HF (gray), its histogram and the Poincare plot.

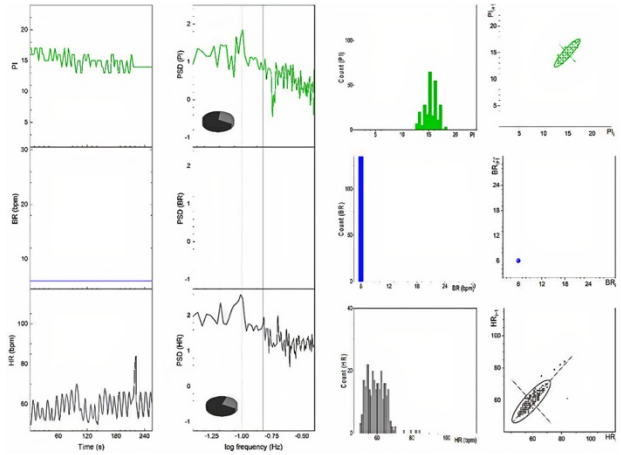

FIGURE 4. Typical physiological time-series records during rhythmically breathing at 0.1 Hz. From top to bottom appears PI, BR and HR. From left to right are the time series, its PSD with vertical lines at 0.15 Hz (continuous) and 0.1 Hz (dotted), and an inlet circle that corresponds to the proportion of LF (black) and HF (gray), its histogram and the Poincare plot. Because BR is constant, there is not PSD and Poincare plot is only one dot.

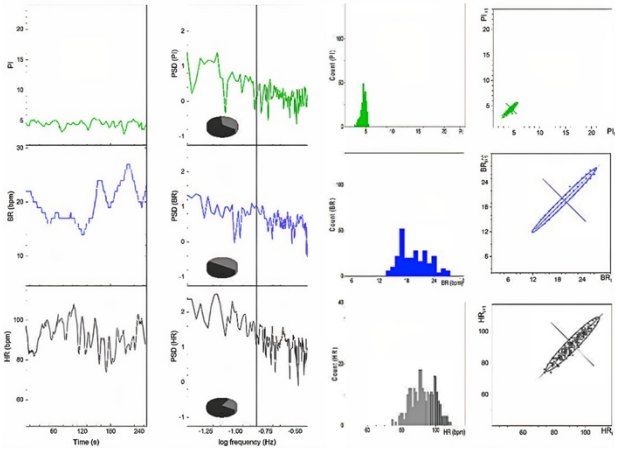

FIGURE 5. Typical physiological time-series records on orthostatism. From top to bottom appears perfusion index (PI), breathing rate (BR) and heart rate (HR). From left to right are the time series, its PSD with a vertical line at 0.15 Hz, and an inlet circle that corresponds to the proportion of LF (black) and HF (gray), its histogram and the Poincare plot.

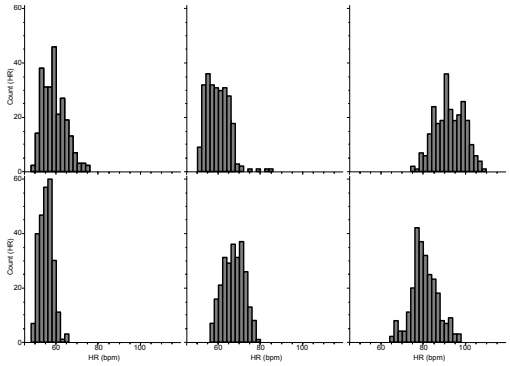

FIGURE 6. Histograms of heart rate under the three maneuvers. From left to right clinostatism, rhythmic breathing at 0.1 Hz, and orthostatism. On top are records from a 19 years old man and on bottom of a woman of the same age.

The different physiological dynamics under the three maneuvers are illustrated on Fig. 3 (clinostatism), Fig. 4 (rhythmic breathing) and Fig. 5 (orthostatism) from the data of a typical day of a 19 years old man. The data from our subjects coincide with previous results [3]: in the temporal domain, clinostatism histograms of HR have a marked asymmetry toward the right-hand side of the distribution (see Fig. 3) reflecting the deceleration capacity of the heart rate as an approximate distinction of vagal and sympathetic effects on the cardiac modulations [25]. In contrast breathing rate and perfusion index are more rigid variables. Breathing rhythmically is confirmed by a constant breathing rate at 6 bpm (thus there is not a Fourier transform and the Poincaré plot is only one dot), producing periodicities on the heart rate due to the fact that the breathing modulation at 0.1 Hz is on resonance with Mayer waves [4], and its clearly seen on Fig. 4 as rigid distribution on PI. Orthostatism is characterized by an increase on heart rate (almost to double values) with higher variability, lowering in perfusion index and less rigid distributions (see Fig. 5). Comparing female vs. male physiological records, we found that clinostatism and orthostatism distributions and Poincaré plots have less variability for females, in agreement with previous results that show that in Fantasia database [6], young females have a more rigid dynamics in comparison with male of similar age (see Fig. 6). Under a strong effort like breathing rhythmically, female and male records are similar. Our current goal is to increase the number of healthy young subjects in our database to generate a benchmark for this noninvasive monitoring of physiological time-series. Changes on the cardio-respiratory variability during the menstrual cycle for women may be due to the presence of hormones like estrogen. Estrogen has multiple vascular effects including alteration of serum lipid concentrations, coagulation, fibrinolysis and the production of vasoactive molecules. Estrogens cause vasodilatation via an effect on endothelial cells, vascular smooth muscle and extracellular matrix, this effect can be related to sympathetic activity, which also has an effect in blood vessels. The estrogen receptors Erα, Erβ and GP30 have been identified in blood vessels of humans, their expression varies with gender, and these receptors are regulated via both genomic and non-genomic pathways [26,27].

CONCLUSIONS

Our study of respiratory and heart rate variability exhibits scale-invariant random fluctuations in all the subjects. Reliable non-invasive biomarkers are statistical moments, entropy, Poincaré plots, and spectral parameters. There is a lack of information regarding the interplay of hormones and cardio-respiratory variability on females, hormones should be taken into account in medical research as this may change the interpretation of variability assessments of health.

ACKNOWLEDGMENTS

We thank the invaluable participation on data acquisition of Vania Navarrete, Daniela Herrera, Maricela Cabrera, Flor Sánchez, Samantha Vazquez, Marelly Salazar, Rodrigo Mendoza, Luis Franceschi and Isaac Chavez. This work was partially funded by: UNAM DGAPA PAPIIT IN113619 and PAPIME PE103519. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. J.C. Toledo-Roy, A.L. Rivera, A. Frank, "Symmetry, criticality and complex systems." *AIP Conf Proc* **2150**, 020014 (2019).
2. R. Fossion R., et al., "A physicist's view of homeostasis" *Physiol Meas* **39**.8, 084007 (2018).
3. A.L. Rivera, et al., "Heart Rate and Systolic Blood Pressure Variability in the Time Domain in Patients with Recent and Long-Standing Diabetes Mellitus." *Plos one* **11**.2, e0148378 (2016).
4. A.L. Rivera, et al., "Loss of Breathing Modulation of Heart Rate Variability in Patients with Recent and Long Standing Diabetes Mellitus Type II." *Plos one* **11**.11, e0165904 (2016).
5. B. Estañol, et al., "From supine to standing: in vivo segregation of myogenic and baroreceptor vasoconstriction in humans." *Physiol Rep* **4**.24, e13053 (2016).
6. A.L. Rivera, et al., "Looking for biomarkers in physiological time series", in *Quantitative Models*, edited by O. Resendiz (Springer, 2018) pp. 111-131.
7. R. Fossion, et al., "On the role of continuous physiological monitoring and time-series analysis in medical prognosis" *AIP Conf Proc* **2090**, 050007 (2019).
8. A. Diaz, M.R. Laufer, and L.L. Breech, "Menstruation in girls and adolescents: Using the menstrual cycle as a vital sign." *Pediatrics* **118**(5), 2245-2250 (2006).
9. O.M. Bazanova, E.D. Nikolenko, and R.J. Barry, "Reactivity of alpha rhythms to eyes opening (the Berger effect) during menstrual cycle phases." *Int J Psychophysiol* **122**, 56-64 (2017).
10. A. Alvergne, Högqvist Tabor V. "Is female health cyclical? Evolutionary perspectives on menstruation." *Trends Ecol Evol* **33**(6), 399-414 (2018).
11. H. Knol, et al. "Haemostatic variables during normal menstrual cycle." *Thromb Haemost* **107**(01), 22-29 (2012).
12. E.H. Yeung, et al. "Longitudinal study of insulin resistance and sex hormones over the menstrual cycle: The biocycle study." *J Clin Endocrinol Metab* **95**(12), 5435-5442 (2010).
13. A.C. Hackney, A.L. Kallman, and E. Ağgön, "Female sex hormones and the recovery from exercise: Menstrual cycle phase affects responses". *Biomed Hum Kinet* **11**(1), 87-89 (2019).
14. L. Espin, et al., "Effects of sex and menstrual cycle phase on cardiac response and alpha- amylase levels in psychosocial stress." *Biol Psychol* **140**, 141-148 (2019).
15. A.D.M. Kashuba, and A.N. Nafziger, "Physiological changes during the menstrual cycle and their effects on the pharmacokinetics and pharmacodynamics of drugs." *Clin Pharmacokinet* **34**(3), 203-218 (1998).
16. A. Weissman, et al. "Modulation of heart rate variability by estrogen in young women undergoing induction of ovulation." *Eur J App Physiol* **105**, 381-386 (2008).
17. M.H. Chung, and C.C.H. Yang. "Heart rate variability across the menstrual cycle in shift work nurses". *J Exp Clin Med* **3**.3, 121-125 (2011).
18. J. A. Johnstone, et al. "Bioharness multivariable monitoring device." *J Sports Sci Med* **11**(3), 400–408 (2012).
19. S. Eckert, and D. Horstkotte, "Comparison of Portapres non-invasive blood pressure measurement in the finger with intra-aortic pressure measurement during incremental bicycle exercise." *Blood Press Monit* **7**(3):179-183 (2002).
20. M. Marshell, et al., "Stratification of fertility potential according to cervical mucus symptoms: achieving pregnancy in fertile and infertile couples." *Hum Fertil* 1-7 (2019).
21. R.J. Fehring, "Accuracy of the peak day of cervical mucus as a biological marker of fertility." *Contraception* **66**(4), 231-235 (2002).
22. J.R. Bull, et al., "Real-world menstrual cycle characteristics of more than 600,000 menstrual cycles." *NPJ digital medicine* **2**(1), 1-8 (2019).
23. S.T. Sims, and A.K. Heather, "Myths and Methodologies: Reducing scientific design ambiguity in studies comparing sexes and/or menstrual cycle phases." *Exp Physiol* **103**(10), 1309-1317 (2018).
24. I.E. Messinis, C.I. Messini, an K. Dafopoulos, "Novel aspects of the endocrinology of the menstrual cycle." *Reprod Biomed Online* **28**, 714-722 (2014).
25. A. Bauer, et al., "Deceleration capacity of heart rate as a predictor of mortality…" Lancet **367**, 1674–1681 (2006).
26. R.A. Khalil, *Cardiovascular & hematological agents in medicinal chemistry* **8**(1), 29–46 (2010).
27. J.O. Machuki, et al., Estrogen regulation of cardiac cAMP-L-type Ca^{2+} channel pathway modulates sex differences in basal contraction and responses to β_2AR-mediated stress in left ventricular apical myocytes. *Cell communication and signaling: CCS*, ***17***(1), 34. (2019).